Wealth of genomic hotspots discovered in embryonic stem cells

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In a paper published in *Cell* on June 13, 2008, Singapore scientists at the Genome Institute of Singapore (GIS) and the National University of Singapore (NUS) unveil an atlas that showing the location of "genomic hotspots" of essential protein "switches" (transcription factors) that are critical for maintaining the embryonic stem (ES) cell state.

Using advanced high throughput sequencing technology, the scientists discovered over 3,000 hotspots. These findings could improve understanding of the unique properties of stem cells that enable them to maintain their intriguing ability to grow and differentiate to virtually any cell type.

"This is the first time such a large scale study has been conducted in Singapore and obtaining such groundbreaking results has caused much excitement," said Wei Chia Lin, Ph.D., Senior Group Leader at GIS. "This blueprint that we obtained is like a treasure map, pointing us to specific sites where we can further study how these switches interact within the cell. Hopefully, this will eventually allow us unlock the secrets of stem cells."

Ng Huck Hui, Ph.D., also a Senior Group Leader at GIS, added, "we think that these 'stemness' hotspots are the most critical points in the genetic blueprint of ES cells. By targeting these hotspots, we may be able to reconnect the wiring in non-stem cells and jump-start the stem cell program in them. This can potentially create an inexhaustible source of clinically useful cells for regenerative medicine or cell based therapies in

the future." The team has already started work to investigate further into this area of research.

"Using cutting edge sequencing technology, scientists from the GIS and NUS have identified hotspots in embryonic stem cells," said Prof. Lee Eng Hin, Executive Director of A*STAR's Biomedical Research Council. "These are important hubs of the genome of embryonic stem cells. This piece of work illustrates how scientists from different disciplines and across institutions can come together to define fundamental features of these intriguing cells."

"In this new paper in *Cell*, the team at the GIS continues their remarkable progress in defining the precise DNA sequences to which an important group of 13 transcriptional factors bind in mouse embryonic stem cells," said Alan Colman, Ph.D., Executive Director of Singapore's Stem Cell Consortium. "This particular group of factors is responsible for maintaining the self renewal and pluripotency of the embryonic stem cells. The team shows that many of the factors which bind to the same gene regions ('hotspots') and their work provide a working model of the transcriptional networks at play within the cells, and how these intracellular networks are linked to events that can be influenced by external stimuli."

The researchers performed genome-wide mapping of the in vivo binding sites for 13 sequence-specific transcription factors in ES cells. These transcription factors play different roles in self-renewal, pluripotency, reprogramming and chromatin insulation. This study uncovers two major modes of binding that give rise to transcription factor co- localization hotspots. The Nanog/Oct4/Sox2 centric hotspots are commonly co-bound by Smad1 and STAT3 and they represent points of integration for the intrinsic and external signaling pathways. The combinatorial wiring of transcription factors is important in deciphering the code behind gene expression program in ES cells.

The work done by the GIS team is a follow up on a series of ongoing research ("The Oct4 and Nanog transcription network that regulates pluripotency in mouse embroynic stem cells," *Nature Genetics* 38:431-440, 2006) into understanding and mapping the transcriptional networks of master genes in ES and somatic cells.

Source: Agency for Science, Technology and Research (A*STAR)